ClinicalEvidence

Polycystic ovary syndrome (PCOS): metformin

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ABSTRACT

INTRODUCTION: Polycystic ovary syndrome (PCOS) is classically characterised by an accumulation of incompletely developed follicles in the ovaries due to anovulation. However, since the publication of the Rotterdam criteria, there is acceptance that menstrual cycle and endocrine dysfunction with hyperandrogenism is more important in reaching the diagnosis than ultrasound findings. It is diagnosed in up to 10% of women attending gynaecology clinics, but the prevalence in the population as a whole varies from 10% to 20%, depending on which diagnostic criteria are used. PCOS has been associated with hirsutism, infertility, acne, weight gain, type 2 diabetes, cardiovascular disease (CVD), and endometrial hyperplasia. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of metformin on hirsutism and menstrual frequency in women with PCOS? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 14 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: metformin compared with placebo/no treatment, metformin compared with weight loss intervention, or metformin compared with cyproterone acetate-ethinylestradiol.

QUESTIONS

INTERVENTIONS

METFORMIN

Likely to be beneficial

Unknown effectiveness

Key points

- Polycystic ovary syndrome (PCOS) is a syndrome of ovarian dysfunction together with established features of hyperandrogenism and morphological polycystic changes in the ovary. It is a condition for which there are disputed diagnostic criterion to confirm clinical diagnosis. However, since the publication of the Rotterdam criteria, there is acceptance that menstrual cycle and endocrine dysfunction with hyperandrogenism are more important in reaching the diagnosis than ultrasound findings.

  Prevalence in the population as a whole varies from 10% to 20%, depending on which diagnostic criteria are used.

  Clinical manifestations of PCOS include infrequent or absent menses and signs of androgen excess, including acne or seborrhoea.

  PCOS has been associated with hirsutism, infertility, insulin resistance, elevated serum luteinising hormone levels, weight gain, type 2 diabetes, CVD, and endometrial hyperplasia.

- In this review, we have reported on the effects of metformin on hirsutism and menstrual frequency in people with PCOS compared with placebo/no treatment, weight loss intervention, or cyproterone acetate-ethinylestradiol.

  We have reported on clinical outcomes, such as hirsutism scores, rather than laboratory-based outcomes (such as effects on hormone levels).

- In general, we found evidence mainly from small RCTs of limited methodological quality.
- Many RCTs reported effects on infertility as their primary outcome, and any data on hirsutism and menstrual effects were more sparingly reported.
- We found limited evidence that metformin may improve menstrual frequency compared with placebo.

  Many of the trials also included a diet or a diet plus exercise intervention in both groups.

- We found insufficient evidence on the effects of metformin on hirsutism compared with placebo.
- Metformin may be associated with an increase of gastrointestinal adverse effects compared with placebo.
- We don't know whether metformin is more effective than a weight loss intervention (diet or diet plus exercise) at improving hirsutism or menstrual frequency.

  We found insufficient evidence from two small RCTs to draw reliable conclusions.

- We don't know how metformin amd cyproterone acetate-ethinylestradiol compare at improving hirsutism and menstrual frequency, as we found little high-quality evidence.

  Metformin may increase gastrointestinal effects (including nausea and diarrhoea) compared with cyproterone acetate-ethinylestradiol, resulting in the need to stop medication.

  However, cyproterone acetate-ethinylestradiol may increase other adverse effects (such as weight gain, high blood pressure, chest pain, and headache) compared with metformin, also resulting in the need to stop medication.

Clinical context

DEFINITION

Polycystic ovary syndrome (PCOS; Stein-Leventhal syndrome; sclerocystic ovarian disease) is, by definition, a condition for which there are disputed diagnostic criteria to confirm clinical diagnosis. It is a syndrome of ovarian dysfunction together with established features of hyperandrogenism and morphological polycystic changes in the ovary. [1] The nomenclature of the condition is somewhat misleading, as the ultrasound findings are not a key part of the diagnostic criteria. Clinical manifestations include infrequent or absent menses and signs of androgen excess, which include acne or seborrhoea. Women with PCOS commonly have insulin resistance and elevated serum luteinising hormone (LH) levels, and are at an increased risk of type 2 diabetes and cardiovascular events. In this review, we have included studies in women aged 18 to 45 years, or where the majority of participants are aged 18 to 45 years.

INCIDENCE/ PREVALENCE

PCOS is diagnosed in 4% to 10% of women attending gynaecology clinics in resource-rich countries, [2] [3] but this figure may not reflect the true prevalence as the criteria used for diagnosis vary. Depending on the diagnostic criteria used, prevalence in the population as a whole varies from 10% to 20%. [4] [5] An international consensus definition of PCOS defined a set of agreed criteria used for diagnosis. [1] Studies since then suggest a greater than 20% incidence and prevalence of PCOS in overweight and obese women. [6]

AETIOLOGY/ RISK FACTORS

The aetiology is unknown. Genetic factors play a part, but the exact mechanisms are unclear. Two studies found some evidence of familial aggregation of hyperandrogenaemia (with or without oligomenorrhoea) in first-degree relatives of women with PCOS. [3] [7] In the first study, 22% of sisters of women with PCOS fulfilled diagnostic criteria for PCOS. [3] In the second study, of the 78 mothers and 50 sisters evaluated clinically, 19 (24%) mothers and 16 (32%) sisters had PCOS. [7] In a study of Dutch women, there was a doubling of the incidence of PCOS in monozygotic twins (though the prevalence was no different to dizygotic twins and the PCOS definition was non-standard). [8] **Diagnosis** The diagnosis excludes secondary causes, such as androgen-producing neoplasm, hyperprolactinaemia, and adult-onset congenital adrenal hyperplasia. [2] It is characterised by irregular menstrual cycles, scanty or absent menses, multiple small follicles on the ovaries (polycystic ovaries), mild hirsutism, and infertility. Many women also have insulin resistance, acne, and weight gain. [2] Until recently, there was no overall consensus on the criteria for diagnosing PCOS. In some studies, it has been diagnosed based on the ultrasound findings of polycystic ovaries rather than on clinical criteria. An international consensus definition of PCOS has now been published, which defines PCOS as at least two of the following criteria: reduced or no ovulation; clinical and/or biochemical signs of excessive secretion of androgens; and/or polycystic ovaries (the presence of at least 12 follicles measuring 2–9 mm in diameter, an ovarian volume in excess of 10 mL, or both). [1]

PROGNOSIS

There is some evidence that women with PCOS are at increased risk of developing type 2 diabetes and cardiovascular disorders secondary to hyperlipidaemia, compared with women who do not have PCOS. [9] A meta-analysis found a twofold increase in the risk of coronary heart disease and stroke in women with PCOS. [10] However, although there is a higher risk of cardiovascular disorders, there is no apparent increase in risk of mortality. [11] There is some evidence that oligomenorrhoeic and amenorrhoeic women are at increased risk of developing endometrial hyperplasia and, later, endometrial carcinoma. [12] [13]

AIMS OF INTERVENTION

To reduce hirsutism and restore regular menstrual cycle, with minimal adverse effects.

OUTCOMES

Hirsutism in women with hirsutism, measured by objective scales of reduction in hirsutism such as the Ferriman-Gallwey Scale, which quantifies the extent of hair growth in nine anatomical sites, scoring 0 (no hair) to 4 (maximal growth), with a maximum score of 36; personal perception of reduction in hirsutism. **Menstruation frequency** in women with oligomenorrhoea. **Adverse effects**. We have also reported on clinical outcomes that matter to people, rather than laboratory-based outcomes such as effects on hormone levels.

METHODS

BMJ Clinical Evidence search and appraisal May 2014. The following databases were used to identify studies for this review: Medline 1966 to May 2014, Embase 1980 to May 2014, and The Cochrane Database of Systematic Reviews 2014, issue 5 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts of the studies identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded for drug interventions. Interventions to achieve weight loss could be unblinded/open. The trials contained 20 or more individuals (10 in each arm), of whom more than 90% were followed up. There was a 3-month minimum length of follow-up for hirsutism outcomes, but no minimum length for other outcomes. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of metformin on hirsutism and menstrual frequency in women with PCOS?**

OPTION **METFORMIN VERSUS PLACEBO OR NO TREATMENT**

- For GRADE evaluation of interventions for Polycystic ovary syndrome (PCOS): metformin, see table, p 15 .
- We found limited evidence that metformin may improve menstrual frequency compared with placebo.
- Some trials also included a diet or a diet plus exercise intervention in both groups.
- We found insufficient evidence on the effects of metformin compared with placebo or no treatment on hirsutism.
- Metformin may be associated with an increase of gastrointestinal adverse effects compared with placebo.

Benefits and harms

Metformin versus placebo (with or without lifestyle intervention):

We found one systematic review (search date 2011), [14] and two additional RCTs. [15] [16] The review pooled data on menstrual frequency but did not report on hirsutism, so we have also reported two RCTs included in the review directly from their original report. [17] [18] The review included RCTs in women with oligomenorrhoea and anovulatory PCOS, and included additional data obtained from some of the original authors of the included RCTs. Several RCTs also included a background dietary or exercise co-intervention in both groups, and where this occurred, we have highlighted this in the study description (see Further information on studies).

Hirsutism

Metformin compared with placebo Metformin may be no more effective than placebo at reducing hirsutism in women with PCOS who are also receiving a low-calorie diet/exercise intervention; however, the evidence was from small, weak RCTs only (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hirsutism					
[15] RCT	40 women, 20 with PCOS, all with BMI >28	**Reduction in Ferriman-Gallwey scores from baseline , 6 months**	No direct comparison between groups		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial	Number of women in this analysis unclear	with metformin with placebo Absolute results not reported The remaining arms evaluated flutamide and metformin plus flutamide All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment	P = 0.022 for change from baseline with metformin P = 0.125 for change from baseline with placebo		
[16] RCT **4-armed trial**	80 overweight or obese women with PCOS, all with BMI >28 The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [15] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited	**Mean reduction in Ferriman-Gallwey scores from baseline , 6 months** 13.0 to 10.9 with metformin 9.3 to 8.0 with placebo The remaining arms evaluated flutamide and metformin plus flutamide All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment	No direct comparison between groups P <0.01 with metformin from baseline P <0.05 with placebo from baseline See Further information on studies		
[16] RCT **4-armed trial**	80 overweight or obese women with PCOS, all with BMI >28 The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [15] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited	**Mean reduction in Ferriman-Gallwey scores from baseline , 12 months** 13.0 to 10.4 with metformin 9.3 to 8.0 with placebo The remaining arms evaluated flutamide and metformin plus flutamide All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment	No direct comparison between groups P <0.01 with metformin from baseline P <0.05 with placebo from baseline See Further information on studies		
[17] RCT	40 women, 20 with PCOS, all with BMI >28 In review [14]	**Reduction in Ferriman-Gallwey score from baseline , 6 months** 14.8 to 12.9 with metformin 11.5 to 10.5 with placebo All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before metformin treatment	No direct comparison between groups P <0.05 with metformin from baseline P value reported as not significant CI not reported for placebo from baseline		
[18] RCT	30 women with PCOS (20–34 years old), with oligomenorrhoea or amenorrhoea In review [14]	**Change in Ferriman-Gallwey score (measured by a modification of Ferriman-Gallwey method; further details not reported) , from baseline–4 months** 11.73 to 11.60 with metformin 13.50 to 13.00 with placebo Results based on 29 women	No direct comparison between groups P = 0.47 with metformin from baseline P = 0.46 with placebo from baseline The RCT reported that it did not find changes in other signs of hyperandrogenism such as acne, seborrhoeic dermatitis, or andro-		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		All women given a nutritional plan of 1500 calories daily plus advice to exercise (40 minutes brisk walking daily, 4 times per week)	genic alopecia; further details were not reported		

No data from the following reference on this outcome. [14]

Menstrual frequency

Metformin compared with placebo Metformin may be more effective than placebo at improving menstrual frequency (not further defined) in women with PCOS who may or may not be also receiving a low-calorie diet/exercise intervention. However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Menstrual frequency					
[14] Systematic review	427 women with PCOS, oligomenorrhoea, or amenorrhoea, mean age in studies about 20–30 years 7 RCTs in this analysis 2 RCTs included co-intervention of lifestyle modification (1 RCT diet [38 women], 1 RCT diet/exercise [143 women])	**Improvement in menstrual frequency (outcome measure not further defined)** 91/207 (44%) with metformin 72/220 (33%) with placebo	OR 1.72 95% CI 1.14 to 2.61 P = 0.01 Significant heterogeneity among RCTs for this analysis (I^2 = 54%, P for heterogeneity 0.03) See Further information on studies	●○○	metformin
[15] RCT **4-armed trial**	40 women, 20 with PCOS, all with BMI >28 Number of women in this analysis unclear	**Improvement in menstrual frequency , 6 months** with metformin with placebo Absolute results reported graphically The remaining arms evaluated flutamide and metformin plus flutamide All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment	P = 0.054 for metformin *v* placebo Menstrual frequency significantly improved from baseline in women taking metformin	⟷	Not significant
[16] RCT **4-armed trial**	80 overweight or obese women with PCOS, all with BMI >28 The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [15] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited	**Increase in mean number of menses , 6 months** 2.6 to 4.3 with metformin 2.7 to 3.2 with placebo 39 women in this analysis The remaining arms evaluated flutamide and metformin plus flutamide All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment	P = 0.031 for metformin *v* placebo See Further information on studies	○○○	metformin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] RCT **4-armed trial**	80 overweight or obese women with PCOS, all with BMI >28 The RCT included 40 women who had their treatment period extended for a further 6 months from an earlier study, [15] which investigated the effect of either drug alone or in combination with dieting, and 40 women who were newly recruited	**Increase in mean number of menses , 12 months** 2.6 to 4.6 with metformin 2.7 to 3.2 with placebo 39 women in this analysis The remaining arms evaluated flutamide and metformin plus flutamide All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before treatment	P = 0.003 for metformin *v* placebo See Further information on studies	○○○	metformin
[17] RCT	40 women, 20 with PCOS, all with BMI >28 In review [14]	**Change from baseline in menstrual frequency , 6 months** 3.5 with metformin 2.2 with placebo All women were given a low-calorie (1200–1400 kcal/day) diet starting 1 month before metformin treatment	P <0.05 This RCT was included in the review [14] but was not included in the meta-analysis for improvement in menstrual frequency We have, therefore, reported the RCT directly from the original report	○○○	metformin

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] Systematic review	23 women with PCOS, oligomenorrhoea, or amenorrhoea, mean age in studies about 20–30 years Data from 1 RCT	**Nausea and vomiting** 5/11 (45%) with metformin 2/12 (17%) with placebo	OR 4.17 95% CI 0.61 to 28.62	⟷	Not significant
[14] Systematic review	92 women with PCOS, oligomenorrhoea, or amenorrhoea, mean age in studies about 20–30 years Data from 1 RCT	**Gastrointestinal disturbance (other than nausea and vomiting)** 15/45 (33%) with metformin 5/47 (11%) with placebo	OR 4.20 95% CI 1.38 to 12.81	●●○	placebo
[14] Systematic review	23 women with PCOS, oligomenorrhoea, or amenorrhoea, mean age in studies about 20–30 years Data from 1 RCT	**Gastrointestinal disturbance (other than nausea and vomiting)** 2/11 (18%) with metformin 0/12 (0%) with placebo	OR = 6.58 95% CI 0.28 to 153.74	⟷	Not significant
[14] Systematic review **Crossover design**	120 women with PCOS, oligomenorrhoea, or amenorrhoea, mean age in studies about 20–30 years Data from 1 RCT	**Gastrointestinal disturbance (other than nausea and vomiting)** 19/60 (32%) with metformin 2/60 (3%) with placebo	OR 27.13 95% CI 6.07 to 121.31 Post-crossover result	●●●	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] RCT	143 anovulatory women with PCOS, BMI >30 In review [14]	**Adverse effects** with metformin with placebo 17 women withdrew from the study because of adverse effects (number of women from each group not reported and adverse effects not specified)			

Further information on studies

[14] The systematic review found significant heterogeneity between the RCTs for menstrual frequency (I^2 54%). It reported a sub-group analysis by BMI for menstrual frequency (participants with BMI <30 kg/m^2: 1 RCT, 23 women, OR 21.15, 95% CI 1.01 to 445.00; participants with BMI 30 kg/m^2 or above: 6 RCTs, 404 women, OR 1.57, 95% CI 1.03 to 2.41, I^2 51%), which did not improve heterogeneity. A sensitivity analysis for menstrual frequency by study quality, which included five RCTs, did not markedly improve heterogeneity or change the inference (further numerical details not reported).

[16] The RCT reported that women were excluded if they were on any medication, if they had a significant change in body weight, or if they were dieting in the previous 3 months. However, it is not clear whether the 40 women from the earlier study had a treatment washout period, whether they continued on the same treatment, or whether they would have received the same treatment after randomisation.

[20] In one RCT included in the review, [14] women taking placebo had a significantly higher BMI at baseline compared with women taking metformin (P <0.05). Women taking placebo also had higher fasting insulin than women taking metformin (P value reported as not significant) but similar insulin sensitivity. This may have biased results in favour of metformin.

Comment: Many RCTs we found reported effects on infertility as their primary outcome, and effects on hirsutism and menstrual patterns were more sparingly reported.

Clinical guide
Weight loss can affect menstrual cycles. In studies where weight loss has occurred as well as taking metformin, we cannot deduce that any improvement in menstrual cycle is only because of the metformin. Those RCTs confuse the issue, and we need to clarify that weight loss might be an independent confounding factor.

OPTION METFORMIN VERSUS CYPROTERONE ACETATE-ETHINYLESTRADIOL

- For GRADE evaluation of interventions for Polycystic ovary syndrome (PCOS): metformin, see table, p 15 .
- We found little high-quality evidence on the comparative effects of metformin and cyproterone acetate-ethinylestradiol on hirsutism or menstrual frequency.
- We don't know how metformin and cyproterone acetate-ethinylestradiol compare at improving hirsutism.
- Some unblinded RCTs found no significant difference between groups with regard to hirsutism scores. However, these data should be interpreted with caution.
- We don't know how metformin and cyproterone acetate-ethinylestradiol compare at improving menstrual frequency.
- Although trials did not directly compare differences between groups, absolute rates of improvement of menses as measured by increased regularity were higher with cyproterone acetate-ethinylestradiol in some RCTs.
- Metformin may be associated with increased gastrointestinal effects (including nausea and diarrhoea) compared with cyproterone acetate-ethinylestradiol, resulting in the need to stop medication.
- Cyproterone acetate-ethinylestradiol may be associated with an increase of other adverse effects compared with metformin, such as weight gain, high blood pressure, chest pain, and headache, resulting in the need to stop medication.

Benefits and harms

Metformin versus cyproterone acetate-ethinylestradiol:

We found two systematic reviews (search date 2005; [21] 2008 [22]). We also found two subsequent RCTs. [23] [24] The first systematic review pooled data on hirsutism, but the RCTs did not meet the quality criteria for this *BMJ Clinical Evidence* review (see Further information on studies). [21] The second systematic review also pooled data on hirsutism at 3 months and 6 months, but the RCTs did not meet the quality criteria for this *BMJ Clinical Evidence* review (see Further information on studies). [22] The first subsequent three-armed RCT compared metformin, cyproterone acetate-ethinylestradiol and cyproterone acetate-ethinylestradiol plus metformin for 3 months. [23] The second subsequent three-armed RCT compared metformin, cyproterone acetate-ethinylestradiol, and rosiglitazone and reported outcomes at 4 months. [24]

Hirsutism

Metformin compared with cyproterone acetate-ethinylestradiol We don't know whether metformin and cyproterone acetate-ethinylestradiol differ in effectiveness at improving hirsutism scores in women with PCOS, as we found insufficient evidence from small, weak RCTs (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hirsutism					
[23] RCT **3-armed trial**	60 women with PCOS Subgroup analysis Women with BMI >25 kg/m^2	**Change in Ferriman-Gallwey hirsutism scores , from pre-treatment to post-treatment** 8.1 to 7.7 with metformin 8.3 to 6.8 with cyproterone acetate-ethinylestradiol Results based on 14/16 (88%) women initially randomised in this sub-group Remaining arm evaluated cyproterone acetate-ethinylestradiol plus metformin	No direct comparison between groups P >0.05 with metformin from baseline P <0.05 with cyproterone acetate-ethinylestradiol from baseline The RCT only reported a subgroup analysis based on initial BMI		
[23] RCT **3-armed trial**	60 women with PCOS Subgroup analysis Women with BMI <25 kg/m^2	**Change in Ferriman-Gallwey hirsutism score , from pre-treatment to post treatment** 7.6 to 7.4 with metformin 7.8 to 6.9 with cyproterone acetate-ethinylestradiol Results based on 23/24 (96%) women initially randomised in this sub-group Remaining arm evaluated cyproterone acetate-ethinylestradiol plus metformin	No direct comparison between groups P >0.05 with metformin from baseline P <0.05 with cyproterone acetate-ethinylestradiol from baseline The RCT only reported a subgroup analysis based on initial BMI		
[24] RCT **3-armed trial**	100 women with PCOS	**Change in Ferriman-Gallwey score , from baseline to 4 months** 12.71 to 10.55 with metformin 15.07 to 12.03 with cyproterone acetate-ethinylestradiol 80 women in this analysis Remaining arm evaluated rosiglitazone	Significance not reported for comparison of metformin *v* cyproterone acetate-ethinylestradiol Both groups significantly improved from baseline (P <0.05)		

Menstrual frequency

Metformin compared with cyproterone acetate-ethinylestradiol We don't know whether metformin and cyproterone acetate-ethinylestradiol differ in effectiveness at improving menstrual regularity in women with PCOS, as we found insufficient evidence from small, weak RCTs (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Menstrual frequency					
[23] RCT **3-armed trial**	60 women with PCOS	**Menstrual regularity (regular menses, not further defined) , at end of trial** 28% with metformin 100% with cyproterone acetate-ethinylestradiol Absolute numbers not reported Definition of menstrual regularity not provided; details of menstrual status at baseline not provided Remaining arm evaluated cyproterone acetate-ethinylestradiol plus metformin	P value not reported		
[24] RCT **3-armed trial**	100 women with PCOS	**Proportion of women with amenorrhoea , from baseline–4 months** 9/47 (19%) to 3/47 (6%) with metformin 7/33 (21%) to 2/33 (6%) with cyproterone acetate-ethinylestradiol Remaining arm evaluated rosiglitazone	Significance not reported for metformin *v* cyproterone acetate-ethinylestradiol		
[24] RCT **3-armed trial**	100 women with PCOS	**Proportion of women with oligomenorrhoea , from baseline–4 months** 29/47 (62%) to 11/47 (23%) with metformin 28/33 (85%) to 0/33 (0%) with cyproterone acetate-ethinylestradiol Remaining arm evaluated rosiglitazone	Significance not reported for metformin *v* cyproterone acetate-ethinylestradiol		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	104 women 3 RCTs in this analysis	**Severe adverse effects requiring stopping of medication (weight gain, high blood pressure, depression, chest pain, headache)** 0/52 (0%) with metformin 10/52 (19%) with cyproterone acetate-ethinylestradiol	OR 0.11 95% CI 0.03 to 0.39 P = 0.00080 Caution should be taken in interpreting these results, as all the RCTs were unblinded (see Further information on studies)	●●●	metformin
[21] Systematic review	104 women 3 RCTs in this analysis	**Severe gastrointestinal adverse effects requiring stopping of medication (nausea, diarrhoea)** 5/52 (10%) with metformin 0/52 (0%) with cyproterone acetate-ethinylestradiol	OR 7.75 95% CI 1.32 to 45.71 P = 0.010 Caution should be taken in interpreting these results, as all the RCTs were unblinded (see Further information on studies)	●●●	cyproterone acetate-ethinylestradiol

No data from the following reference on this outcome. [23] [24]

Further information on studies

[21] Hirsutism: the review included pooled data on hirsutism for three RCTs. However, all the RCTs were unblinded, and it did not perform an ITT analysis. It found no significant difference between metformin and cyproterone acetate-ethinylestradiol in hirsutism using the Ferriman-Gallwey (FG) scoring system (2 RCTs, analysis included 35/52 [67%] of women initially randomised, mean difference +2.66, 95% CI –0.33 to +5.66, P = 0.081). One other RCT found a significant improvement with metformin using a subjective (VAS 0–10) hirsutism score (1 RCT, analysis included 34/52 [65%] of women initially randomised, mean difference 2.70, 95% CI 0.99 to 4.41, P = 0.0019). In this RCT, all women had an FG score above eight at baseline. A further analysis including all three RCTs found no significant difference between groups in hirsutism (FG and subjective) score (3 RCTs, analysis included 69/104 [66%] of women initially randomised, SMD –0.18, 95% CI –0.67 to +0.32, P = 0.48). There was significant heterogeneity among RCTs for this analysis (I^2 80%, P for heterogeneity = 0.01).

[21] Menstrual frequency: the review also provided a pooled analysis of two unblinded trials which found that metformin was significantly less effective at improving menstrual pattern (2 RCTs, analysis included 35/52 [67%] of women initially randomised, OR 0.08, 95% CI 0.01 to 0.45, P = 0.0042).

[22] Methods: the most recent review included eight RCTs. Of these, five RCTs had unclear randomisation, six RCTs did not use blinding, allocation concealment was either not used or unclear in six RCTs, and withdrawal rate varied from 0% to 44%.

[22] Hirsutism: the review reported pooled data on hirsutism at 3 months. Although it did not directly identify the two RCTs included in the analysis, in another table it identified two unblinded RCTs that reported outcomes at 3 months. However, it is not clear whether it was these RCTs included in the analysis or not. It found no significant difference between metformin and cyproterone acetate-ethinylestradiol in hirsutism (3 months, FG score: 2 RCTs, 42 women, mean difference –2.12, 95% CI –4.78 to +0.53, P = 0.12, absolute numbers not reported). It also reported no significant difference between groups at 6 months or longer (FG score: 3 RCTs, 69 women, mean difference +0.49, 95% CI –1.92 to +2.91, P = 0.69). This analysis included the same three RCTs pooled by the other review for hirsutism. [21] Again, there was significant heterogeneity among RCTs (I^2 83%, P for heterogeneity = 0.002).

[22] Menstrual frequency: the review did not report data on this outcome.

Comment: Cyproterone acetate-ethinylestradiol is associated with an increased risk of venous thromboembolism. [25]

OPTION METFORMIN VERSUS WEIGHT LOSS INTERVENTION

- For GRADE evaluation of interventions for Polycystic ovary syndrome (PCOS): metformin, see table, p 15 .
- We found insufficient evidence, from two small RCTs, to draw reliable conclusions on how metformin compares to a weight loss intervention in regulating the menstrual cycle and on symptoms of hirsutism.

Benefits and harms

Metformin versus weight loss intervention:

We found one systematic review (search date 2011), which compared lifestyle modification programmes (modification of diet and/or physical activity) with metformin in women with PCOS. [26] The systematic review did not report pooled data on our outcomes of interest. We have, therefore, reported two RCTs included in the review that matched the quality criteria for this *BMJ Clinical Evidence* review from their original reports. [27] [28] The first RCT compared metformin with a 1200–1400 kcal diet (25% proteins, 25% fat, 50% carbohydrates, plus 25–30 g of fibre per week; see Further information on studies). [27] The second RCT was a four-armed trial. [28] We have reported the two arms that compared metformin with a lifestyle intervention, which comprised a low-calorie diet (500 calories less than daily requirements) plus an exercise programme (in accordance with a prescribed rehabilitation menu, 3–5 times per week, each time for 20–60 minutes). See Further information on studies. Many RCTs that compared metformin with placebo or no treatment also included diet and/or exercise in both groups as a background intervention (see Metformin versus placebo or no treatment, p 3).

Hirsutism

Metformin versus weight loss intervention We don't know whether metformin and a diet intervention (1200–1400 kcal diet) differ in effectiveness at improving hirsutism scores in women with PCOS (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hirsutism					
[27] RCT	46 women with PCOS, aged 19–38 years, mean BMI about 32 kg/m^2, mean duration of infertility about 5.2–5.4 years In review [26]	**Proportion of women with hirsutism (measure of hirsutism not further defined) , before and after treatment** 16/22 (73%) to 13/22 (59%) with metformin 15/24 (63%) to 13/24 (54%) with diet intervention	P value between groups not reported See Further information on studies		

No data from the following reference on this outcome. [28]

Menstrual frequency

Metformin versus weight loss intervention We don't know whether metformin differs from a weight loss intervention (a diet intervention or a diet plus exercise intervention) in effectiveness at improving menstrual frequency in women with PCOS (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Menstrual frequency					
[27] RCT	46 women with PCOS, aged 19–38 years, mean BMI about 32 kg/m^2, mean duration of infertility about 5.2–5.4 years In review [26]	**Menstrual cycle pattern (regular/irregular; further definition not reported) , after treatment** with metformin with diet intervention Absolute results not reported	Reported as no significant difference P value not reported Unclear as to which data this analysis relates to See Further information on studies	⟷	Not significant
[27] RCT	46 women with PCOS, aged 19–38 years, mean BMI about 32 kg/m^2, mean duration of infertility about 5.2–5.4 years In review [26] Subgroup analysis Women with irregular cycle at baseline	**Resumption of regular cycles (proportion of women going from having irregular cycle to resumption of regular cycles) , 6 months** 11/18 (61%) with metformin 13/21 (62%) with diet intervention These data exclude 3/24 (13%) of women with weight loss intervention and 4/22 (18%) of women with metformin who had regular menstrual cycle at baseline	Reported as no significant difference P value not reported See Further information on studies	⟷	Not significant
[28] RCT **4-armed trial**	343 women with PCOS, mean age 27 years, mean infertile period 3.9–4.5 years among 4 groups In review [26] The 4 arms were metformin (90 women), lifestyle (75 women), clomiphene citrate	**Improvement rates of menstrual cycle (further definition of outcome measure not reported)** 56% with metformin 67% with lifestyle modification Absolute numbers not reported	P value not reported for direct comparison of metformin *v* lifestyle modification See Further information on studies		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(90 women), and clomiphene citrate plus metformin (88 women)				

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[27]	46 women with PCOS, aged 19–38 years, mean BMI about 32 kg/m^2, mean duration of infertility about 5.2–5.4 years In review [26]	**Diarrhoea** 21% with metformin Five women (21%) complained of diarrhoea of 2–3 weeks' duration in the metformin group; further details not reported			

No data from the following reference on this outcome. [28]

Further information on studies

[27] The RCT did not report on weight loss directly, but reported changes in BMI during the trial (before and after treatment: 31.9 to 27.8 kg/m^2 with metformin *v* 32.2 to 27.4 kg/m^2 with diet intervention; reported as both groups had significant reduction from baseline, no between-group analysis reported). Randomisation was by table of random numbers, but details of allocation concealment and levels of blinding were unclear. It reported that both treatments were continued until the woman resumed the first regular cycle (within 24–35 days of treatment), and when there was no resumption or evidence of ovulation, both treatments were continued for 6 months.

[28] Before women could be included in this RCT they needed to have achieved a 5% weight loss, as this was needed to start menstrual cycles. It is not clear how this would have affected the results of the study. The RCT did not describe methods of randomisation, allocation concealment, or blinding. The RCT did not report on weight loss or changes in BMI, but reported that waist circumference was significantly lowered in the diet and exercise group compared with the other three groups (P = 0.001; no further details reported).The 5% weight loss that was achieved may have affected the results of the study, especially menstrual regularity.

Comment: None.

GLOSSARY

Ferriman-Gallwey Scale Hirsuitism scale that quantifies the extent of hair growth in nine anatomical sites, scoring 0 (no hair) to 4 (maximal growth), with a maximum score of 36.

Hirsutism The presence of excessive male-pattern hair growth in women on the face, chest, linea alba, or lower back. It usually occurs in women with polycystic ovary syndrome (PCOS), but 'idiopathic hirsutism' may occur in women with regular menstrual cycles and normal circulating androgen levels.

Oligomenorrhoea Infrequent or scanty menstruation.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Metformin versus cyproterone acetate-ethinylestradiol Option restructured to include only the comparison of metformin versus cyproterone acetate-ethinylestradiol. New evidence added. [22] [23] [24] Categorised as 'unknown effectiveness'.

Metformin versus placebo or no treatment Option restructured to include only the comparison of metformin with placebo or no treatment. New evidence added. [14] [18] Categorised as 'likely to be beneficial'.

Metformin versus weight loss intervention Option restructured to include only the comparison of metformin with weight loss intervention. New evidence added. [26] [27] [28] Categorised as 'unknown effectiveness'.

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GRADE **Evaluation of interventions for Polycystic ovary syndrome (PCOS): metformin.**

Important outcomes **Hirsutism, Menstrual frequency**

Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of metformin on hirsutism and menstrual frequency in women with PCOS?									
4 (unclear; no more than 190) [15] [16] [17] [18]	Hirsutism	Metformin versus placebo (with or without lifestyle intervention)	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness points deducted for no direct statistical analysis between groups and for co-intervention (diet)
9 (546) [14] [15] [16] [17]	Menstrual frequency	Metformin versus placebo (with or without lifestyle intervention)	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results; consistency point deducted for statistical heterogeneity among RCTs; directness point deducted for co-intervention (diet)
2 (117) [23] [24]	Hirsutism	Metformin versus cyproterone acetate-ethinylestradiol	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for no statistical analysis between groups
2 (unclear; no more than 140) [23] [24]	Menstrual frequency	Metformin versus cyproterone acetate-ethinylestradiol	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness points deducted for no statistical analysis between groups in 1 RCT and unclear outcome in 1 RCT
1 (46) [27]	Hirsutism	Metformin versus weight loss intervention	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness points deducted for no direct statistical analysis between groups and unclear outcome measurement
2 (unclear) [27] [28]	Menstrual frequency	Metformin versus weight loss intervention	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods; directness point deducted for unclear outcome measurement

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.